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Clearance of topically-applied PVP-iodine as a solution or gel in periodontal pockets in men

Sahrmann, Philipp ; Sener, Beatrice ; Ronay, Valerie ; Attin, Thomas ; Schmidlin, Patrick R

Abstract: **OBJECTIVES** The aim of the study was to investigate the clearance of PVP-iodine applied as a gel or solution in periodontal pockets. **METHODS** Teeth of 12 subjects with at least eight periodontal pockets of 5 mm probing depth were isolated with a rubber dam to allow contamination-free access to the pockets. In each subject, three pockets were filled with PVP-iodine gel (10%) and three with PVP-iodine solution (10%). One pocket of each subject without iodine application served as a negative control. The treatment allocation was assigned randomly. Any excess material was removed subsequently. After 1, 5 and 15 min, a paper point was used to collect the sulcus liquid and the concentration of PVP-iodine was chemically determined. In addition, PVP-iodine gel was administered into 12 periodontal pockets immediately after sub-gingival ultrasound debridement and the concentration of PVP-iodine was determined after 1 min. **RESULTS** Descending concentrations of PVP-iodine were determined at 1, 5 and 15 min after the application. No PVP-iodine was found in the pockets serving as negative controls. The mean concentrations of the gel and solution were 6.14 g/ml and 4.44 g/ml (1 min; $p = 0.028$), 3.20 g/ml and 1.44 g/ml (5 min; $p = 0.126$), 0.69 g/ml and 0.23 g/ml (15 min; $p = 0.019$), respectively. In the pockets with previous debridement the mean concentration was 1.68 ± 1.97 g/ml. **CONCLUSION** The application of PVP-iodine gel in periodontal pockets allows a prolonged remnant effect as compared to that of the solution formula.

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Clearance of topically applied PVP-iodine as solution or gel in periodontal pockets in men

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Running title: Clearance of PVP-iodine

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Keywords: Povidone-iodine, clearance, antiseptics, periodontal disease

Abstract

Background: Data on the clearance of topically applied antiseptics like PVP-iodine in periodontal pockets are weak. Therefore, the aim of the study was to investigate the clearance of PVP-iodine applied as a gel or solution in periodontal pockets.

Design: Teeth of 12 subjects with at least 8 periodontal pockets of ≥ 5 mm were isolated with rubber dam allowing contamination-free access to the pockets. In each subject, three pockets were filled with PVP-iodine gel (10%) and three with PVP-iodine solution (10%). One pocket of each subject without iodine application served as a negative control. The treatment of the pockets was randomly assigned. Any excess material was removed. After 1, 5 and 15 min, a paper point was used to collect the sulcus liquid and the concentration of PVP-iodine was chemically determined. In addition, PVP-iodine gel was administered into 12 periodontal pockets immediately after subgingival ultrasound debridement and the concentration of PVP-iodine was determined.

Results: Descending concentrations of PVP-iodine were determined at 1, 5 and 15 min after the application. No PVP-iodine was found in the control pockets. The mean concentrations of the gel and solution were 6.14 $\mu\text{g/ml}$ and 4.44 $\mu\text{g/ml}$ (1 min; $P \geq 0.028$), 3.20 $\mu\text{g/ml}$ and 1.44 $\mu\text{g/ml}$ (5 min; $P \geq 0.126$), 0.69 $\mu\text{g/ml}$ and 0.23 $\mu\text{g/ml}$ (15 minutes; $P \leq 0.019$), respectively. In the pockets with previous debridement the mean concentration was $1.68 \pm 1.97 \mu\text{g/ml}$.

Conclusion: The application of PVP-iodine gel in periodontal pockets allows a prolonged remnant effect as compared to that of the solution formula.

Introduction

Periodontitis is a common infection-induced inflammatory disease resulting in a progredient destruction of the periodontal fiber apparatus and alveolar bone with subsequent apical migration of the junctional epithelium.[1-4] Bacterial plaque accumulation is considered as the primarily etiologic factor.[5, 6] Consequently, periodontal therapy focusses on the elimination of biofilms and subgingival calculus on the root surface. The use of curettes and ultrasonic devices is a well documented and effective treatment modality.[7, 8] In addition, various attempts to eliminate pathogenic bacteria by additively administered chemical means have been undertaken: Systemically administered antibiotics proved significant effectiveness in combination with scaling and root planing[9-12] but bear the risk of undesirable side-effects and the development of bacterial resistance.[13] Topical application of antiseptics in periodontal pockets as an adjunctive to the mechanical debridement has been suggested[14-18] and tested in various clinical trials.[19, 20]

Among these topically administered pharmaceuticals, PVP-iodine is an antiseptic with a broad antibacterial spectrum covering Gram-positive and -negative bacteria and mycobacteria,[21] *Staphylococci spp.* and *Candida albicans*,[22] and anaerobic bacteria commonly considered as periodontal pathogens such as *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans* and *Fusobacterium nucleatum*. [23, 24] Therefore, it has a broad field of application in general medical practice and dentistry.[25-29] Although several studies showed additional short-term improvements when PVP-iodine was used during subgingival debridement, studies are discordant about the degree of PVP-iodine's additional effect. A recent systematic review on this topic proved evidence for an improved therapeutical effect regarding pocket depth reduction, when PVP-iodine was used during scaling and root planing.[30]

Control of periodontal microbiota by any antimicrobial agent is dependent on the

concentration and period of exposure. Therefore, prolonged clearance of PVP-iodine has been considered as an important factor improving its clinical efficacy.[31]

Data on the clearance of topically applied PVP-iodine in periodontal pockets is scarce. However, a few reports on the clearance of agent vehicles have been published.[19, 32] Therefore, the aim of the present study was to investigate the clearance of PVP-iodine in either solution or gel form applied in the periodontal pockets with and without instrumentation. We hypothesized that a gel formulation demonstrates prolonged periods of clearance.

Materials and Methods

Subjects

12 patients, 8 male and 4 female, with a generalized, severe periodontitis were randomly selected from patients frequenting the department due to initial periodontal treatment. They were informed about the study design and the study's aim and participated voluntarily in this study. The study was conducted in accordance to the Declaration of Helsinki and approved by the ethics committee of the University of Zurich (SPUK, StV 07/16). All participants were generally healthy, none of them was pregnant or showed thyroid disorders. None of them was allergic to iodine-compounds. Each patient included had at least eight teeth with probing depths ≥ 5 mm in either the upper or lower jaw.

Patient selection and sampling was carried out by the same investigator (PS) (see Fig. 1).

Clinical sampling

Prior to the sampling, the teeth including the gingival sulcus were isolated using a rubber dam (Dental Dam Latex, Roeko, Langenau, Germany), which was glued to the alveolar mucosa with histoacrylic glue (Histoacrylkleber, B. Braun, Sempach, Switzerland). Thus, a contamination-free access into the pockets was enabled (Fig.1).

Seven pockets ≥ 5 mm were numbered consecutively and treated according to a computer generated randomized list (compiled by PRS), that defined the allocation of the pockets that were to be measured after different application modalities. The treatment allocation was kept in a sealed envelope that was opened after the patient's agreement to the study, directly before treatment. In each subject, one pocket served as a control site: that pocket was left without any manipulation prior to sampling. Three pockets were filled with PVP-iodine gel (10%) and three with PVP-iodine solution (10%) (both Mundipharma, Basel, Switzerland) (Fig. 2). The filling process was performed gently with a blunt syringe of an inner diameter of 0.49 mm (Endo-EZE tip, Ultradent, UT, USA) until PVP-iodine gel/solution was supragingivally visible. Care was taken not to provoke any bleeding. Any excess material was cautiously removed with a foam pellet (Pele Tim®, VOCO, Cuxhafen, Germany) directly before sampling, carefully avoiding any pressure on the gingiva in order not to squeeze out the material left in the pocket.

After 1, 5 and 15 min, a paper point (paper points #40, taper 0.02, Roeko, Langenau, Germany) was inserted deeply into one pocket each. The paper tip was left for 10 s in the sulcus until it was soaked with the sulcus fluid. Immediately afterwards it was placed into an individually labelled gas-tight Eppendorf tube, weighted and afterwards stored in a fridge at 5°C before the chemical analysis was performed within three days. Hence, each pocket was only measured once.

During the study, patients were blinded to the allocation of the different applications. Fig. 3 shows the flowchart of enrollment, allocation and analysis.

In addition, one further periodontal pocket of each subject was mechanically treated by conventional scaling and root planing prior to the application of PVP-iodine gel. Sampling was performed after 1 min as described above. Bleeding on sampling was visually controlled and recorded.

Iodine determination

Eppendorf tubes with one dry paper point each were prepared and labelled individually. Before and immediately after the sampling, their weights were determined using a high precision accuracy scale (AT 261 DeltaRange, Mettler-Toledo, Greifensee, Switzerland). The amount of absorbed sulcus liquid was determined by calculating the weight difference.

The quantitative chemical analysis of PVP-iodine was performed according to the acid digestion.[33] The terminatory quantitative analysis was performed according to the method of Sandell-Kolthoff (1937),[34] modified by Groppel (1987): This methodological approach allows to unlock PVP-iodine compounds in the sample and to transform elementary iodine into a less volatile iodide. This iodide serves as a specific catalysator in a titration reaction of a definite amount of cerium with arsenic trioxide, which discolours the former yellow solution. The grade of discolourization is directly proportional to the amount of iodine in the solution and can be quantified by measuring the translucency of the solution. A double-beam spectrophotometer (U2010, Hitachi medical systems, Zug, Switzerland) was used to measure the translucency absorption at a peak at 405 nm.

Statistical analysis

The statistical analysis was carried out using StatView[®] 4.02 (Abacus Concepts, Berkeley, CA, USA). The results were presented as box-plots. Normal distribution was tested using a Kolmogorov-Smirnov test. Kruskal-Wallis one-way test of variance followed by Wilcoxon signed rank tests for individual comparison were used and a Bonferroni-adjustment was applied for multiple testing. For all statistical analyses, $p < 0.05$ was considered to be statistically significant.

Results

Patient characteristics concerning gender, age and bleeding-on-sampling are given in Table 1. Information concerning the characteristics of the investigated pockets like pocket depth and bleeding-on-sampling are listed in Table 2. No adverse side effects on rubber dam or povidone was recorded. Among the groups with sampling at different time points no remarkable differences in pocket depth were found. PVP-iodine concentrations (mean \pm SD) are presented in Fig. 4.

PVP-iodine was detectable at 1, 5 and 15 min with descending concentrations for both application forms. No PVP-iodine was detectable in the control pockets. Statistically significant differences were found between different time points and, comparing solution and gel, a tendency after 1 and 5, and a significant difference after 15 min due to a higher residual concentration of the gel formulation (Figure 3).

No differences concerning the pocket characterization were observed between solution and gel. Bleeding on sampling was recorded in 11% of the sampling sites. In these cases, though bleeding was hardly visible to the naked eye, PVP-iodine concentration ranged below the confidence interval that was calculated for the whole collective. After 1 min, the concentrations of PVP-iodine in the pocket reached a value of about 50% of the initial concentration for both solution and gel.

For the pocket that had been scaled 1 minute previously, PVP-iodine was still detectable in all the samples but the concentration values ranged at about only 1.7 $\mu\text{g/ml}$. In each of these pockets a manifest bleeding was observed.

Discussion

We recorded a decreasing concentration during the observation period for both application forms of PVP-iodine, gel and solution, in periodontal pockets. After 1 min, concentration values ranged at approximately 50% of the initial concentration. After 5 min the concentrations of both applications forms were still around 5 µg/ml and after 15 min slightly above the detection limit at 0.1µg/ml. Comparing solution and gel, there was a strong tendency for a higher residual concentration of the gel form after 1 and 5 min. After 15 min, the difference between solution and gel was statistically significant.

The confidence intervals for the results were quite broad. This is in accordance with findings of Oosterwaal et al.[35] who also found large variations with an analog study design and reported, that „*not all pockets reacted in the same way*“. Indeed, there is a large spectrum of confounding factors like different pocket depths and a different pocket anatomy of different tooth types on the one hand, and bleeding out of the pocket on the other hand. In addition, the chemical determination of PVP-iodine is a complex, technique sensitive multiple-staged procedure inflicting a couple of risk factors to the analysis. Still, regarding the sample size we decided to rely on previous studies investigating the same topic.

To minimize these factors, we made sure to fulfill all three tenets for the correct measurement of gingival crevicular fluid, a measurement quite similar in quality and quantity to our aim, as postulated by Goodson[36]: Firstly, calibration of the measuring instrument by weighting of the paper tips and use of a calibrated accuracy weighting machine, secondly the isolation of the pockets by rubber dam and finally the maintenance of a dry, non irritated gingiva.

In order to achieve a quick, technically easy and reliable measurement of sulcus liquid we decided to use paper points rather than micropipettes or capillary tubing as an alternative – but less suitable - sampling method[37]. For the measurement of the amount of liquid in the samples, we relied on the mass weighting using a high precision accuracy weighting machine.

This technique has recently been shown to be the more exact measurement as compared to a metric analysis of the stained area on the paper points [38].

The time points for sampling were chosen with regard to a former study on clearance of fluorescein in periodontal pockets of humans[35] and a further study investigating the clearance of a technetium-99m formulation by gamma scintigraphy in humans, that covered a clearance rate of 75% of the initial concentration.[32]

Five minutes after application we found PVP-iodine concentrations in the pockets that have been proven to eliminate planktonic periodontal pathogens *in vitro*. [22, 39] After 15 minutes PVP-iodine was still detectable in most of the pockets, but the mean concentration ranged at about a tenth of the initial value (0.1µg/ml). Whether this concentration is effective against biofilms *in vivo* is in question: The same concentration of 0.1µg/ml has been found by Schreier et al.[21] to be PVP-iodine's efficacy maximum in an *in vitro* study investigating the bactericidal effect of PVP-iodine against *Staphylococcus aureus*, *Candida albicans* and *Escherichia coli*. However, bacteria imbedded in the biofilm with its protective and adhesive extracellular matrix are less susceptible to antiseptics.[40] Accordingly, clinical conclusions cannot be drawn.

Comparing the clearance values in our study with the findings of Oosterwaal et al.,[35] who reported a 50% concentration of the initial value after a time of 12.5 minutes, the results seem contradicting. Oosterwaal et al., on the other hand, pointed out, that within the first five minutes most of the gel disappeared from the pockets. Actually, they specify that the 50% clearance within a period of 12.5 min that was described in their results does not begin until 5 min after the application of their solution. In fact, within the first minutes a clearance curve with a comparable, much quicker concentration loss is shown in that study: within the first 60 s a clearance of about 50% is detectable within the figure describing the concentration loss of fluorescein over time.

Within the shortcomings regarding the complexity of sampling and analysis, the results of this study indicate that a concentration of PVP iodine may be maintained over several minutes in periodontal pockets. A considerable limitation for the clinical impact in periodontal therapy is shown by the low concentrations of PVP-iodine, if the pockets previously had been scaled. Apparently, bleeding increased the pocket clearance in a way that iodine was hardly detectable after one minute.

Further studies should investigate the effect of PVP-iodine in forms with a lower clearance rate in periodontal therapy.

Conclusion

The results of this study indicate, that a PVP-iodine concentration of 3.2 µg/ml and 1.6 µg/ml for a gel formulation and a solution, respectively, may be sustained over a period of five minutes after application into non-scaled periodontal pockets.

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Conflict of interests

The authors declare that they have no conflict of interest related to the present study.

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Figure legends:

Fig. 1 Applied and glued rubberdam, inserted paper points

Fig. 2 Application and measurement of PVP-iodine as gel or solution

Fig. 3 Flowchart of allocation, enrollment and analysis

Fig. 4 Box plot of different concentrations of solution and gel at different times

Fig. 1 Applied and glued rubberdam, inserted paper points

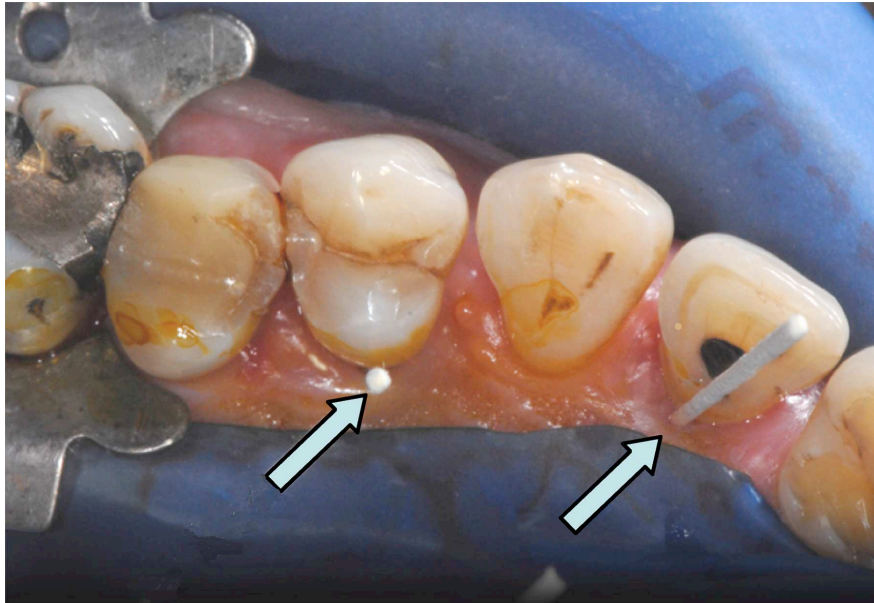
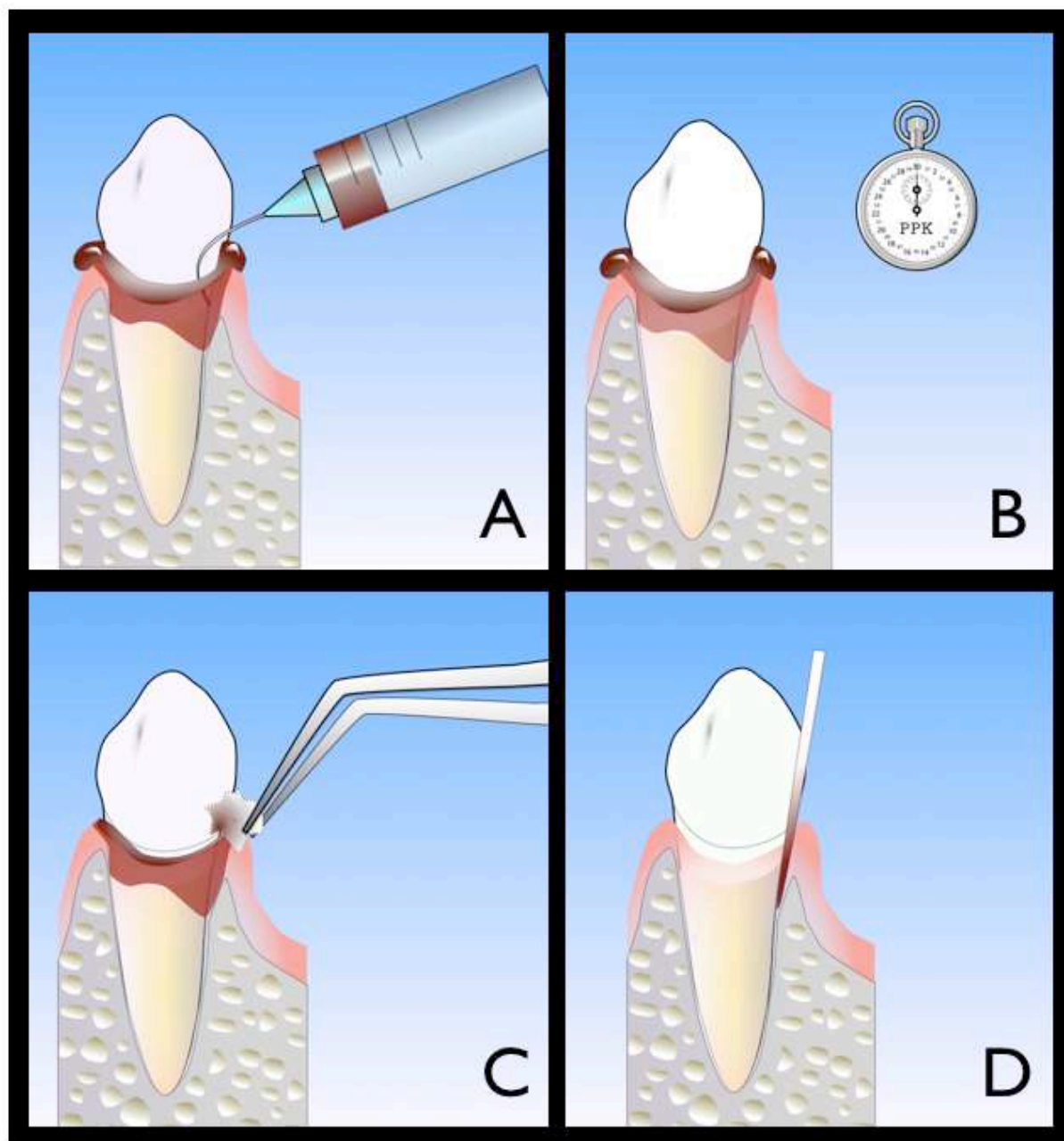


Fig. 2 Application and measurement of PVP-iodine as gel or solution



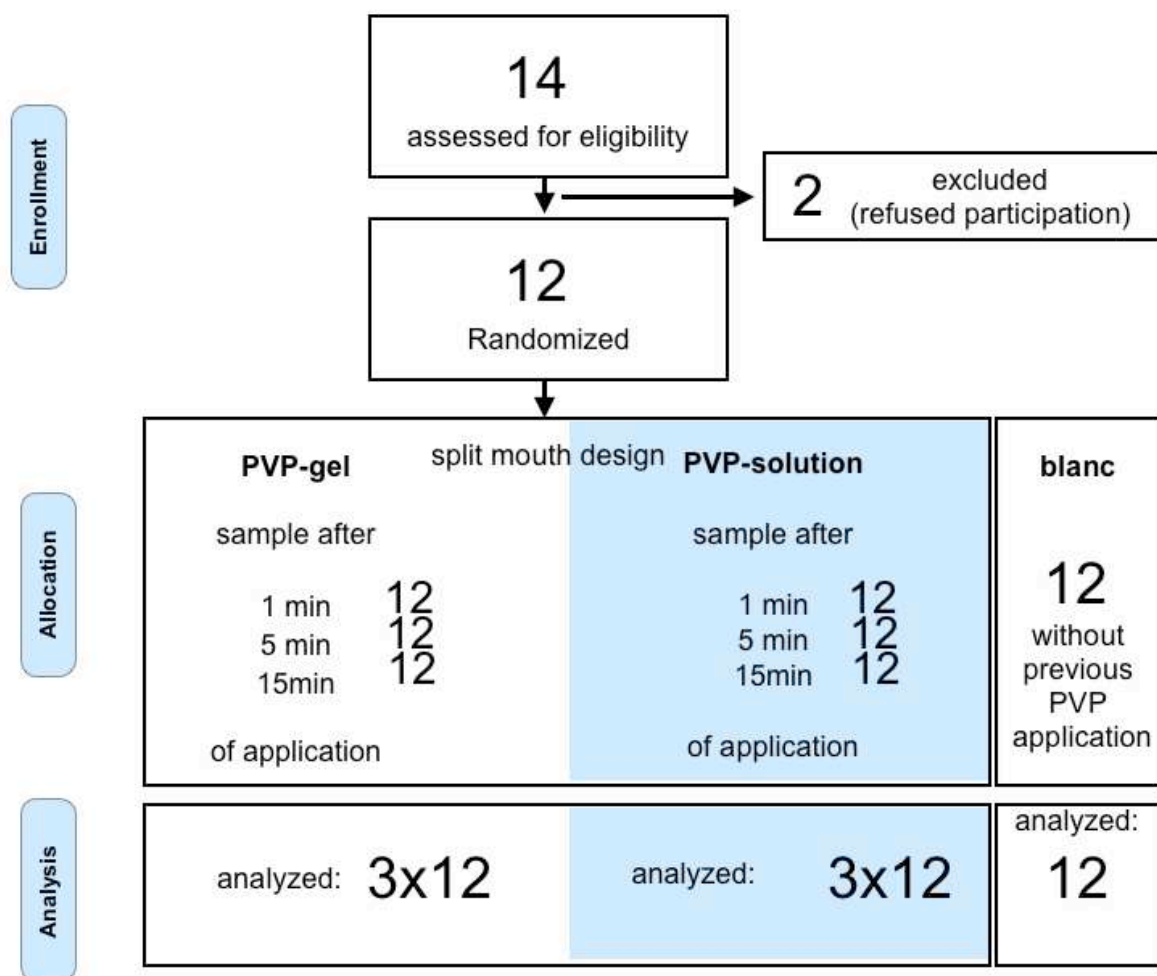
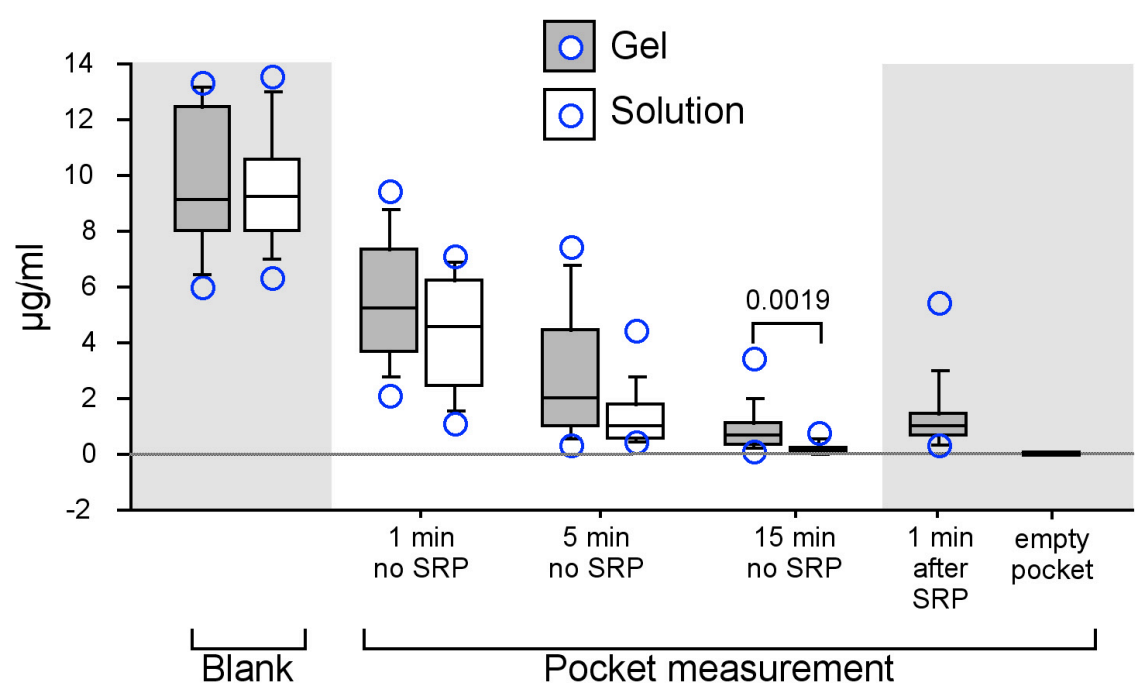


Fig. 3 Enrollment, allocation and analysis of the samples

Fig. 4 Box plot of different concentrations of solution and gel at different times



Legend: SRP – Scaling and Root planing

Table 1 Patient characteristics

Nr.	Initials	Gender	Age [y]	ØPPD [mm]
1	ED	M	45	5.9
2	MS	M	66	6.4
3	BF	M	43	6.1
4	RK	M	34	5.1
5	HS	M	38	7.3
6	CV	F	45	5.4
7	SN	F	47	5.4
8	GG	M	50	6.9
9	GM	M	42	6.3
10	BB	F	34	6.0
11	EJ	M	42	5.1
12	JB	F	40	7.0

Legend: M – male

F – female

PPD – Periodontal Probing Depth of the investigated teeth

Table 2 Pocket characteristics

Time points	Solution			Gel		
	Periodontal Pocket Depth		Bleeding Sites	Periodontal Pocket Depth		Bleeding Sites
	Mean \pm SD			Mean \pm SD		
	$[\mu\text{g/ml}]$	Min, Max		$[\mu\text{g/ml}]$	Min, Max	
1 min	6.1 ± 0.9	5, 8	2/12	5.8 ± 0.7	5, 7	3/12
5 min	5.9 ± 0.5	5, 7	1/12	5.9 ± 1.0	5, 8	0/12
15 min	5.8 ± 0.7	5, 7	3/12	5.8 ± 0.8	5, 7	1/12

Legend: SD – Standard deviation